Remarks

In response to the Restriction Requirement dated October 2, 2003, applicants elected Group I, claims 1-5 and 20-26, and the species of SEQ ID NO:1. Claim 2 was cancelled. Claims 1, 3, 5, 20 and 25 were amended to reflect the election of Group I (antisense) and SEQ ID NO:1. Claim 22 was previously cancelled, and claims 1, 3-5, 20, 21 and 23-26 are pending. No new matter is added.

Claims 1, 3-5 and 20-26 were rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of written description in the specification. Applicants previously traversed this rejection on the grounds that by providing the sequence of KIAA0175 polynucleotide (SEQ ID NO:9) they have provided written description for oligonucleotides capable of hybridizing with SEQ ID NO:9. This is not a situation wherein one of skill must provide missing information; on the contrary, all the possible antisense oligonucleotides are contained within the disclosed sequence and are therefore written in the application.

In the response filed on July 31, 2003, applicants argued that this situation is distinguishable from the written description issues described by the Court of Appeals for the Federal Circuit in The Regents of the University of California vs. Eli Lilly and Company, 119 F.3d 1559 (C.A.F.C. 1997) wherein the Court held that the name "cDNA" is not itself written description of DNA, in the absence of sequence information indicating which nucleotides constitute human cDNA for insulin. In the present case, the sequence information is provided in SEQ ID NO:9.

In response to applicants' arguments, the Examiner stated that Branch (TIBS 23:45-50, 1998) supports the position that "not all complementary nucleotides can serve as antisense molecules." (Office Action, page 5, lines 4-5.) The Examiner further stated "[t]he fact that one can randomly choose complimentary polynucleotides to hybridize a particular target sequence does not allow them to envision which of these molecules will exhibit an antisense function." (Office Action, page 5, lines 11-14.)

The Branch reference actually supports applicants' position that by providing the polynucleotide sequence of KIAA0175, applicants have satisfied the written description within the technical constraints of antisense technology. Contrary to the Examiner's suggestion, Branch

supports a position that written description in the antisense field is not an appropriate hurdle to have to overcome, because one of skill in the art would not expect a patentee to have provided "on paper" a suitable antisense molecule. (Branch, page 49, paragraph bridging columns 2-3.)

This position is distinguishable from the Regents case discussed above; in that case, one of skill in the art was not provided with a written polynucleotide sequence for the claimed cDNA for human insulin. The human insulin cDNA "on paper" was not evident from or contained in the sequence in the patent disclosure. In the present situation, the sequence of each possible antisense molecule is evident from the disclosed polynucleotide sequence. Although the Examiner has focused on Branch's comments about the alleged unpredictability of antisense technology, Branch concludes that "there is growing evidence that antisense molecules can be useful pharmaceutical tools when applied carefully." (Page 50, last paragraph.) Branch also refers to the "time and expense" necessary to screen antisense candidates, but does not state that this is outside the scope of the experimentation one of skill would expect to perform in this art.

Regarding the Examiner's statements about gene therapy in paragraph 3, at pages 8-10, the Examiner again cited Branch and Jen (Stem Cells 18:307-319, 2000). To demonstrate the amount of experimentation allegedly necessary to identify a useful antisense molecule, Branch duplicates a figure originally reported by Monia *et al.* (Nature Medicine 2:668-675, 1996). A review of the Monia article directly, rather than depending on Branch's interpretation, reveals that it in addition to describing a screen for antisense oligonucleotides, Monia *et al.* also provides an excellent example of the successful use of antisense molecules *in vitro* and *in vivo*. Monia *et al.* tested a number of oligonucleotides in order to attain the specific reduction of C-*raf*-1 kinase mRNA in cancer cells. While more than 35% of antisense oligonucleotides showed a "moderate" reduction in C-*raf*-1 kinase mRNA (Monia at page 669, left column), one of the test oligonucleotides had a "potent" (Monia at page 669, left column) five-fold effect on C-*raf*-1 kinase mRNA levels in cancer cells. Monia *et al.* further demonstrated that the addition of this antisense oligonucleotide to cultured cancer cells markedly inhibited cell proliferation, and that intravenous administration of a C-*raf*-1 kinase antisense molecule to tumor-bearing mice resulted in a significant inhibition of tumor progression. In all cases, a mismatched antisense

oligonucleotide control was found not to have any effect on C-*raf*-1 kinase mRNA levels or cell proliferation.

Contrary to Branch's characterization, Monia et al. did not describe any of their experimentation as excessive or undue, and in fact several of their antisense constructs were biologically active, although they chose to focus on the most active one for further experimentation. Branch dismisses the non-"potent" antisense constructs, i.e. those that did not show at least a five-fold effect, but neither Branch nor the Examiner explains why an effect of this magnitude is necessary. There is no evidence in Branch or in Monia that antisense constructs having some specific biological activity are not equally useful. Applicants therefore submit that the Examiner's reliance on Branch, and on Jen, who reaches similar conclusions, is at odds with the original publications of antisense experimental results.

Furthermore, another example of the successful use of antisense molecules *in vivo* is provided by Nakashima *et al.* (Arch. Otolaryngol. Head Neck Surg. 126:957-961, 2000), who used athymic nude mice to test cyclin D1 antisense molecules. These authors reported that the administration of cyclin D1 antisense molecules resulted in a reduction of cyclin D1 mRNA and protein expression. Further, they reported in vivo studies in which cancer cells were injected into athymic nude mice with or without antisense cyclin D1. The mice that were injected with cancer cells *with* antisense cyclin D1 exhibited tumors 84-99% smaller than those found in the control mice.

These cases support the argument that antisense technology, while involving experimentation to identify appropriate antisense molecules, is capable of reliably producing a specific, objective therapeutic effect.

Claims 1, 3-5 and 20-26 were rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. The Examiner cited the Ex parte Forman (230 U.S.P.Q. 546 (Bd. Pat. App. & Inter. 1986)) and In re Wands (8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988)), factors in support of this ground of rejection. In the Office Action dated December 24, 2003, the Examiner found that the applicants' arguments were not persuasive. The Examiner's comments are addressed herein.

1. *Quantity of experimentation necessary.* Applicants previously asserted that one of ordinary skill in this art can routinely generate and use antisense oligonucleotides that are based upon the sequence of KIAA0175, provided herein as SEQ ID NO:9. The inventors have identified that antisense oligonucleotides capable of specifically binding to a KIAA0175 polynucleotide can affect biological processes that depend on KIAA0175 activity. The KIAA0175 protein product possesses an autophosphorylation activity that can be assayed, as described in the specification, Example 2 at pages 37-38. Thus, an objective test exists for measuring KIAA0175 activity. The specification also provides a method for detecting changes in KIAA0175 mRNA levels following administration of an antisense oligonucleotide, in Example 4, pages 39-40. The specification further discloses methods of measuring cell viability following transfection with an antisense oligonucleotide of the invention, and exposure of cells to irradiation or chemotherapeutic agents (Examples 8 and 9).

To determine if a polynucleotide falls within the scope of the claims, therefore, only the performance of cell transfection and assay procedures is required, with measurement of an objective outcome. These procedures are routine and would not have to be done repeatedly before a clear result was obtained. Because the inventors and the art provide means for the objective measurement of the biological effect of a polynucleotide falling within the claim scope, this factor is met. These biological effects include mRNA levels, and cell viability following exposure to a DNA-damaging agent or treatment.

The Wands court stated that an "experiment" was not simply the screening of a simple hybridoma, but instead was the entire attempt to make a monoclonal antibody against a particular antigen. This process included immunizing animals, fusing lymphocytes from the immunized animals to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas. (8 USPQ2d at 1406.)

By analogy, a single experiment in the present art could include obtaining or constructing an antisense oligonucleotide based on SEQ ID NO:9, conducting experiments as disclosed in Example 4, and measuring KIAA0175 mRNA levels. Another experiment could include transfection of cells with an antisense oligonucleotide of the invention, exposing the cell to an agent having use as a DNA-damaging agent, and measuring cell viability, as described in

Examples 8 and 9. Encountering negative results would not mean that undue experimentation is involved, according to Wands.

The Examiner asserts, in response, that "undue and unpredictable trial and error experimentation" would be required, but provides no support for this assertion. Branch in fact indicates that workers in this art do perform screening of "large numbers of candidates" for their ability to act inside cells. (Branch, page 49, left column, center paragraph.) Although Branch focuses on the "40%" that had almost no effect, this implies that 60% did have an effect. The Branch reference also poses an example of screening 20-50 candidates, and although the author states that this may be "time-consuming and expensive" (page 49, second-third columns), she does not state that this experimentation is "undue and unpredictable," contrary to the Examiner's characterization of the experimentation. Branch's statement that tests of 50 molecules could identify good candidates (page 49, right column) suggests the opposite conclusion, under Wands.

2. *Amount of direction or guidance provided.* The specification provides clear directions for performing the experimentation (including Examples 4, 8, and 9). Similarly, the Wands court found that the starting material was available to the public (as is the material used in the present application) and the patent at issue in Wands provided a detailed description of the methods, which included use of a commercially available kit. (8 USPQ 2d at 1404, 1405). The cell lines used in applicants' methods are commercially available, and the application describes the methods, at pages 39-47. The claims recite antisense inhibitors of KIAA0175 mRNA. Such inhibition is measured, for example, by assaying the mRNA of cells exposed to the antisense molecules, such as described in Example 4. The claims recite compositions, not methods.

In reply to this argument, the Examiner maintains the position that the relevant nature of the invention is gene therapy. This conclusion is at odds with the state of the art as reflected in Branch's publication. Branch states that the relationship between *in vitro* and *in vivo* activity is an active area of research. Thus, applicants' statements that the examples in the specification do provide the guidance for experimentation are consistent with the state of the art at the time of filing. Branch does not suggest that *in vitro* examples and results "do not test the relevant nature of the invention." In fact, Branch specifically states that "because it is very

difficult to predict what portions of an RNA molecule will be accessible *in vivo,* effective antisense molecules must be found empirically by screening a large number of candidates for their ability to work inside cells." (Page 49, left column, last paragraph.) This is precisely what applicants have disclosed, and what is permitted under Wands.

3. *Presence of absence of working examples.* The specification describes transfection of HT1080 cells using a claimed polynucleotide of the invention, specifically KIAA 0175 antisense oligonucleotides (pages 39-40). The experiment provides an example that is applicable to other claimed KIAA0175 anti-sense oligonucleotides (test polynucleotides), which would be used to transfect the HT 1080 cells. The inhibition of KIAA0175 mRNA would signal that the test polynucleotide is within the scope of the claims. The specification also describes measuring cell viability in cells transfected with an antisense molecule of the invention, and exposing the cells to a known DNA-damaging agent or treatment (pages 45-47).

In reply to applicants' arguments, the Examiner states that "antisense gene therapy must be enabled" and that the "problematic" basic scientific principles persist even in the absence of a gene therapy use for the invention. (Pages 9-10, Office Action.) Applicants addressed the alleged problematic aspects of antisense technology in Section 2 above with cites to Branch. In Jen et al., Stem Cells 18:307-319 (2000), the authors indicate that systems are available to determine the accessibility of sequences within mRNA transcripts that are suitable for antisense targeting, citing Scherr, M. et al., Nuc. Acids Res. 26:5079-5085 (1998) and Scherr, M. et al., Nuc. Acids Res. 28:2455-2461 (2000). The 2000 article addresses computer-assisted selection. Both articles were published near or before the time of filing the present application and can be relied upon because they establish knowledge in the art. Both publications are cited on the accompanying form and copies are submitted herewith. The articles address and refute the alleged inability to accurately predict the sequence of antisense oligonucleotide that will bind to an accessible region of target mRNA.

Regarding the allegedly problematic non-antisense effects of nucleotide sequences, Branch uses the term "diamond mine" in this context (page 45, right column), so the Examiner's characterization of this as a purely "problematic" principle is not accurate. Furthermore, Branch suggests that a non-antisense effect can be countered by using "numerous

control ODNs when carrying out antisense research." (Page 46, right column.) Branch was published in 1998, so this information can be considered within the knowledge of those skilled in the art when this application was filed.

4. *Nature of the invention.* KIAA0175 is the name given to a protein having homology to yeast Rad53. In yeast, Rad53 is essential in the control of entry of cells into the S phase of the cell cycle, which is the phase of DNA synthesis. Rad53 is also phosphorylated and activated in response to DNA damage (specification at page 5, line 18 through page 6, line 3). Thus, KIAA0175 plays a role in DNA synthesis during the cell cycle, and in facilitating DNA repair after damage such as by irradiation and chemical agents. Applicants believed that inhibition of KIAA0175 could have implications in the ability of a cell to survive damage to its DNA. As DNA damage is a goal of many therapies, such as γ-irradiation and chemotherapy for cancer, applicants sought a means for inhibiting KIAA0175. One such means is provided by the antisense oligonucleotides and methods disclosed in the application.

To fulfill its biological role, KIAA0175 protein expression increases following exposure of cells to DNA-damaging agents such as γ-irradiation or hydroxyurea (specification at page 6, lines 14-16). By inhibiting KIAA0175 gene expression, it is possible to abrogate the cell cycle arrest that is associated with such treatment, abolishing the damage repair, and leaving cells *vulnerable* to the cytotoxicity of these therapeutic DNA damaging agents (specification at page 7, lines 15-18). Antisense inhibitors of KIAA0175 have numerous utilities, including *in vitro* inhibition of KIAA0175 protein expression in cells, thereby allowing one of skill to test radiation and chemotherapeutic agents for their cytotoxic effects in the cells with and without functional KIAA0175. Such methods are disclosed, for example, at page 23, line 9 through page 24, line 4.

Applicants respectfully submit that the Examiner has inappropriately focused on gene therapy as the utility of the invention as claimed. Applicants strongly disagree with this limited characterization of the invention. On the contrary, the invention is useful in testing radiation and chemotherapeutic agents for their effect on cells *in vitro*. This aspect of the invention must be taken into account when evaluating enablement under the Wands factors. The invention relates to human polynucleotides. Methods of synthesizing, isolating, mutating,

manipulating, transfecting, and expressing polynucleotide are the basis for the biotechnology industry. The nature of the invention is such that it is well-known to those of ordinary skill in the art. The court in Wands stated that the nature of monoclonal antibody technology is such that it involves screening (in that case, hybridomas). The present invention provides antisense molecules, contrary to the Examiner's statements at page 9, lines 8-12.

Applicants previously asserted that the nature of the invention relates to the ability of KIAA0175 inhibitors, in this instance, antisense oligonucleotides, to sensitize cells to DNA-damaging agents such as γ-irradiation, hydroxyurea, and other potentially useful chemotherapeutic agents. Such an effect can be tested as clearly described in the specification, for example at pages 44-45 (Examples 8 and 9). Example 8 clearly describes the transfection of HCT116 cells with KIAA0175 antisense molecules or control molecules. The cells are then treated with the DNA-damaging method or composition of choice, such as γ-irradiation or hydroxyurea. Viability is assessed at specified days after treatment, and the extent of viability correlates with the ability of the antisense treatment to sensitize the cells to the DNA-damaging agent. The ability of KIAA0175 antisense oligonucleotides to sensitize cells to chemotherapeutic agents, radiation, or other putative DNA-damaging agents can be assessed in this manner *in vitro* (Examples 8 and 9). Such results can then be used to guide decisions about treatment of an organism.

For the foregoing reasons, applicants continue to urge that the nature of the invention is much broader than the limited scope suggested by the Examiner, namely, gene therapy. Viewing the nature of the invention in the light described in this section, it is indisputable that undue experimentation is not required to practice the invention and to identify antisense oligonucleotides within the scope of the claims.

The Examiner responded to applicants' foregoing arguments by stating that the cited references establish a state of the art as it relates to antisense technology. Applicants have reviewed the cited references above, and concur that the nature of the invention is antisense technology. If the Examiner interpreted any of the statements in applicants' previous response as asserting that the invention is not drawn to antisense technology, applicants wish to clarify herein that antisense oligonucleotides are the subject of the present claims.

5. *The state of the prior art.* The state of the art is such that, similar to the art discussed in Wands, those of skill expect to conduct experimentation to achieve positive results. The new information that the inventors bring to the field relates to the identity of the gene to be inhibited by the antisense molecules as claimed, and not to antisense technology and procedures generally. The prior art provides the methods and materials needed to apply the methods of factor (4) above to this group of oligonucleotides, specifically KIAA0175 antisense oligonucleotides. The Wands court found that "all the methods needed to practice the invention were well-known." (8 USPQ 2d at 1406). Similarly, the methods of transfecting cells, expressing mRNA, measuring mRNA levels, and assessing cell vitality are well known, as evidenced by the specification and by the references cited by the Examiner. The Examiner asserts that the state of the art for gene therapy is the standard to which the present invention applies. Applicants disagree, for reasons discussed in paragraph (4) above. The alleged problems with gene therapy include, according to the Examiner, the vectors used for gene therapy (page 10, lines 16-17), for example. These broader problems are not addressed by, nor are they intended to be addressed by, the current invention.

In response to applicants' arguments, the Examiner stated that "the state of the art teaches that the invention is unpredictable" and that the instant invention must overcome the alleged deficiencies in order for the skilled artisan to make and use the invention. Applicants submit that the overall conclusion presented in the cited art is not that the invention is unpredictable. On the contrary, the cited art provides ample evidence that, at the time of filing, one of the skill in this art had access to and knowledge of techniques for addressing and overcoming the alleged unpredictability. The cited art is analyzed above, and relevant points include:

a. One of skill expects to screen a large number of candidates for their ability to act inside cells. (Branch, p. 49, first column, last paragraph.)

b. In a screen of 34 antisense molecules, 3% were "highly effective" and 40% had "almost no effect," with 60% having some effect. (Branch, page 49, columns 1-2.)

c. Non-antisense effects are not *per se* unwanted (Branch, Jen).

d. Methods for mRNA site selection were publicly available in 1998 (Jen, page 313, left column, last paragraph).

Points (a) and (b) are entirely consistent with the Wands court's approval of experimentation to achieve positive results.

6. *The relative skill of those in the art.* Those of skill in this art are highly skilled and would be competent at designing and performing, or directing the performance of, the procedures of factors (4) and (5) above. The Wands court found that the level of skill in the monoclonal antibody was high at the time the application was filed, but, importantly, the court also found that *development of skill* in performing specific experiments relevant to the art did not preclude enablement. Specifically, the court stated that initial failures occurred as the inventors learned to fuse cells, and "[o]nce they became skilled in the art, they invariably obtained numerous hybridomas . . ." that met the claim limitations. (8 USPQ 2d at 1406). By analogy, it would not defeat enablement for one of skill in the art of antisense transfection and expression to learn and become proficient in techniques for practicing the present invention. Applicants reiterate that it is not the responsibility of the present inventors to teach those of skill how to overcome the alleged deficiencies of gene therapy in general.

Contrary to the Examiner's assertions in the present Office Action, Applicants did not specifically state that one of skill would be able to reasonably predict that any nucleic acid complimentary to KIAA0175 would serve as an antisense molecule. The cited references (Branch, Jen) establish in fact that such prediction was not expected at the time of filing. Instead, one of skill can apply the methods of the invention (specifically, determining if KIAA0175 antisense molecule inhibits mRNA, and measuring the effect of such inhibition on cell susceptibility to radiation or chemotherapeutic damage) and utilize the appropriate controls and amount of experimentation taught by the prior art to achieve suitable antisense molecules.

7. *The predictability or unpredictability of the art.* One of skill, being acquainted with the methods described in the application, would predict that when a KIAA0175 antisense molecule was transfected into HT1080 cells, the inhibitory effect on KIAA0175 mRNA would be objectively detectable. The person of skill, testing other polynucleotides as claimed, would predict that the outcome would reflect the ability of the test polynucleotide to

hybridize with KIAA0175 polynucleotide in the cell, and that this would be the primary variable affecting the results. Those of skill are prepared to use appropriate control experiments to limit the effect of the variability of experimental conditions on the results.

In Wands, the Court noted that the cell fusion technique was well known to those of ordinary skill in the art, and that there was no indication that the fusion step would be more difficult or unreliable for the antigen in question (HBsAg) than for other antigens. Transfection of a cell and measuring the level of KIAA0175 mRNA is taught in the present specification, and the Examiner has provided no evidence that the transfection step would be "more difficult or unreliable" (8 USPQ2d at 1406) than for other anti-sense molecules.

Applicants disagree with the Examiner's characterization of the skilled artisan as being unable to make an antisense nucleic acid because he or she did not know what it looks like in terms of a structure-function relationship. The structure of an antisense molecule is known: it is an oligonucleotide of about 17-25 nucleotides in length complementary to mRNA of KIAA0175. This is not a case of an unknown chemical structure with a variety of R groups, bonds, and the like. Applicants teach a representative number of antisense molecules having exactly the desired structure/function. Applicants teach how to test function using methods that were successfully applied to the representative antisense molecules. Applicants teach how to routinely test for other molecules within the scope of the claims. The Wands court required no more.

8. *The breadth of the claims.* Using materials and methods routinely available at the time of filing, one of skill can routinely identify or construct any nucleic aid molecule meeting the limitations of the claims, and test it for activity as described for the previous factors.

All of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

If questions remain regarding this application, the Examiner is invited to contact the undersigned at (206) 628-7650.

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